Autonomic modulation of myocardial microvascular responses and blood flow during sevoflurane anesthesia

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Chapter 6

General anesthesia with sevoflurane decreases myocardial blood volume and hyperemic blood flow in healthy humans

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ABSTRACT

Background

Preservation of myocardial perfusion during general anesthesia is likely important in patients at risk for perioperative cardiac complications. Data related to the influence of general anesthesia on the normal myocardial circulation are limited. In this study we investigated myocardial microcirculatory responses to pharmacological vasodilation and sympathetic stimulation during general anesthesia with sevoflurane in healthy humans immediately prior to surgical stimulation.

Methods

Six female and seven male subjects (mean age 43, range 28 – 61) were studied at baseline while awake and during the administration of 1 minimum alveolar concentration sevoflurane. Using myocardial contrast echocardiography, myocardial blood flow (MBF) and microcirculatory parameters were assessed at rest, during adenosine-induced hyperemia and after cold pressor test-induced sympathetic stimulation. MBF was calculated from the relative myocardial blood volume multiplied by its exchange frequency (β) divided by myocardial tissue density (ρT), which was set at 1.05 g ml^{-1}.

Results

During sevoflurane anesthesia, MBF at rest was similar to baseline values (1.05±0.28 versus 1.05±0.32 ml min^{-1} g^{-1}; *P*=0.98; 95% confidence interval [CI] -0.18 to 0.18). Myocardial blood volume decreased (*P*=0.0044; 95% CI 0.01 to 0.04) while its exchange frequency (β) increased under sevoflurane anesthesia when compared to baseline. In contrast, hyperemic MBF was reduced during anesthesia compared to baseline (2.25±0.5 versus 3.53±0.7 ml min^{-1} g^{-1}; *P*=0.0003; 95% CI 0.72 to 1.84). Sympathetic stimulation during sevoflurane anesthesia resulted in a similar MBF compared to baseline (1.53±0.53 and 1.55±0.49 ml min^{-1} g^{-1}; *P*=0.74; 95% CI -0.47 to 0.35).

Conclusions

In otherwise healthy subjects that are not subjected to surgical stimulation, myocardial blood flow at rest and after sympathetic stimulation is preserved during sevoflurane anesthesia despite a decrease in myocardial blood volume. However, sevoflurane anesthesia reduces hyperemic myocardial blood flow, and thus myocardial blood flow reserve, in these subjects.

INTRODUCTION

Myocardial blood flow (MBF) is meticulously matched to oxygen demand by complex interactions of metabolic, endothelial and neural factors.[1,2] General anesthesia may interfere with this regulatory process by influencing the determinants of myocardial blood flow, such as coronary vascular resistance (CVR), myocardial oxygen consumption or perfusion pressure.[3] Understanding the mechanisms of myocardial perfusion regulation during general anesthesia is important in patients at risk for perioperative cardiac complications, particularly those with coronary artery disease. Experimental research has demonstrated that volatile anesthetics are coronary vasodilators with different effects on hemodynamic parameters and myocardial perfusion.[4-7] Clinical studies are ambiguous, reporting either increases or decreases in coronary vascular resistance and overall myocardial perfusion after exposure to inhalational anesthetics.[8-11]

Until recently, the lack of noninvasive, bedside imaging techniques impeded investigation of MBF in the perioperative setting. Accepted techniques such as single-photon emission computed tomography or positron-emission tomography are non-portable and involve exposure to radiation. Myocardial contrast echocardiography (MCE) is a safe, noninvasive bedside tool that may provide a unique opportunity to investigate myocardial microvascular responses during general anesthesia.[12] The technique has been validated under experimental conditions and against the aforementioned "gold standards" for MBF measurements.[13-16] MCE enables quantification of absolute MBF from its microvascular constituents, the relative myocardial blood volume (rBV) and its exchange frequency (β) which corresponds to the capillary blood exchange rate.[14] Because 90% of the myocardial blood volume resides within the capillary network, rBV mainly represents the blood volume at the capillary level.[17]

Regulation of MBF and microvascular function may be evaluated by two contrasting interventions. Pharmacological coronary vasodilation allows assessment of the vascular smooth muscle-dependent increase in MBF while sympathetic stimulation by the cold pressor test (CPT) evaluates the endothelium-dependent increase in MBF. In this study we investigated myocardial microcirculatory responses to pharmacological vasodilation and sympathetic stimulation during general anesthesia with sevoflurane in healthy humans immediately before surgical stimulation.

METHODS

Subjects

This prospective, observational clinical study was approved by the local Human Subjects Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands (www.clinicaltrials.gov; NCT00866801). All thirteen included subjects (6 women, 7 men;

mean age 43 ± 11 years) were scheduled for general anesthesia and gave written informed consent. Exclusion criteria were a history of cardiac or pulmonary disease, hypertension, hypercholesterolemia, diabetes mellitus and allergic reactions to echocardiographic contrast agents. All patients were ASA class I and had a normal physical examination and resting electrocardiogram. None of the subjects received medications known to interfere with myocardial blood flow measurements. Routine transthoracic echocardiography (TTE) revealed no abnormalities except for mild asymptomatic aortic insufficiency in one patient. Standard cardiovascular autonomic function tests (heart rate variability at rest and during deep breathing, heart rate and blood pressure response to the Valsalva maneuver and postural change) were performed to exclude the presence of autonomic dysfunction.[18]

Study protocol

All subjects were scheduled for an extra visit to our hospital for screening and baseline MBF measurements. These were performed several days before the surgical procedure to avoid surgery-related anxiety and stress that might influence the results. On the day of surgery, MBF measurements were repeated after induction of anesthesia and before the start of the surgical procedure. All subjects refrained from caffeine and xanthine derivatives 12 hours prior to MBF measurements.

Assessment of myocardial blood flow

TTE was used to perform MCE for measurement of MBF at rest and following adenosine-induced hyperemia and CPT-induced sympathetic stimulation. A sulphur hexafluoride-filled, phospholipid-coated ultrasound contrast agent with a mean microbubble diameter of 2.5 μm (Sonovue, Bracco Imaging, Milan, Italy) was used for flow measurements. Microbubbles were infused continuously at a rate of 0.5-0.7 ml min^{-1}.[19] After a steady and homogenous distribution of contrast was reached, rest perfusion sequences were acquired from transthoracic apical 4-, 2- and 3-chamber views. Subsequently, hyperemia was induced by a continuous infusion of adenosine (0.14 mg kg^{-1} min^{-1}). Two minutes after starting the adenosine infusion another series of perfusion sequences was obtained. Five minutes after discontinuing the adenosine infusion, sympathetic stimulation was provoked by the CPT, which is performed by immersing the hand of the patient in ice water (2-4˚C) for 3 minutes. A similar series of perfusion sequences was captured directly after the CPT. Heart rate, blood pressure and electrocardiogram were obtained at predetermined times throughout the protocol.

Anesthetic procedure

On arrival in the operating room patients received standard hemodynamic monitoring (pulse oximetry, electrocardiogram and noninvasive blood pressure measurement). All subjects were administered 0.02 mg kg^{-1} midazolam via an intravenous cannula inserted in a forearm

vein. Anesthesia was induced by inhalation of sevoflurane (Abbott B.V., Hoofddorp, The Netherlands) and maintained at 1.0 MAC during the study period, which took on average 20 minutes. After insertion of a laryngeal mask airway, MBF measurements were performed in left lateral position during spontaneous breathing without positive airway pressure and a FiO_2 of 100%. End-tidal CO_2 was observed to be between 35-45 mmHg. After the study protocol, anesthesia and the surgical procedure were continued according to standard of care.

Myocardial contrast echocardiography

Acquisition

Real-time MCE was performed using an iE33 ultrasound scanner equipped with a S5-1 sector array transducer and contrast-specific software (Power modulation, Philips Medical Systems, Best, The Netherlands). Settings included a mechanical index (MI; the acoustic intensity of an ultrasound beam) of 0.17 for microbubble detection, MI of 0.64 for microbubble destruction, dynamic range of 47 dB and linear postprocessing for minimal distortion of the original input values.[19] MBF was calculated from a destruction-replenishment sequence consisting of 5 cardiac cycles of low MI imaging (steady state), followed by a short burst (0.5 seconds) of high MI for complete myocardial contrast destruction. Subsequently, 15 cardiac cycles of low MI images were acquired to allow myocardial contrast replenishment. All data were stored for offline analysis.

Data analysis

Quantification of MBF was performed as described previously.[19] In short, perfusion sequences were analyzed using custom-designed software with manual tracking of region of interest (ROI) (Figure 1). Using only end-systolic frames, ROIs were drawn in accordance with the vascular territories of the coronary arteries in the mid-inferoseptal and mid-anterolateral wall (apical 4-chamber view); in the mid-inferior and mid-anterior wall (apical 2-chamber view) and in the mid-inferolateral and mid-anteroseptal wall (apical 3-chamber view) of the myocardium. Additional ROIs were drawn in the left ventricular cavity, adjacent to the myocardial ROI. Subsequently, the obtained signal intensities were linearized by removing logarithmic compression and intensity data were expressed in arbitrary units. Myocardial steady state intensity A_{myo} was calculated by averaging the myocardial intensity data extracted from the end-systolic frames before contrast destruction. Left ventricular intensity A_{LV} was determined by averaging all ventricular intensities except in the end-systolic frames during and the first two after contrast destruction. Dividing plateau intensity A_{myo} by the left ventricular intensity A_{LV} yielded the rBV. Finally, β (min^{-1}) was derived from fitting of the refill equation $y(t) = A_{myo} \cdot (1 - e^{-\beta \cdot t})$ by Wei *et al.* to the myocardial intensity data after microbubble destruction.[13] The capillary exchange rate β provides an estimate of the speed of erythrocytes through the capillary system. A slower or faster capillary passage, indicated by a decrease or increase in β, is consistent with arteriolar vasoconstriction or dilation respectively.

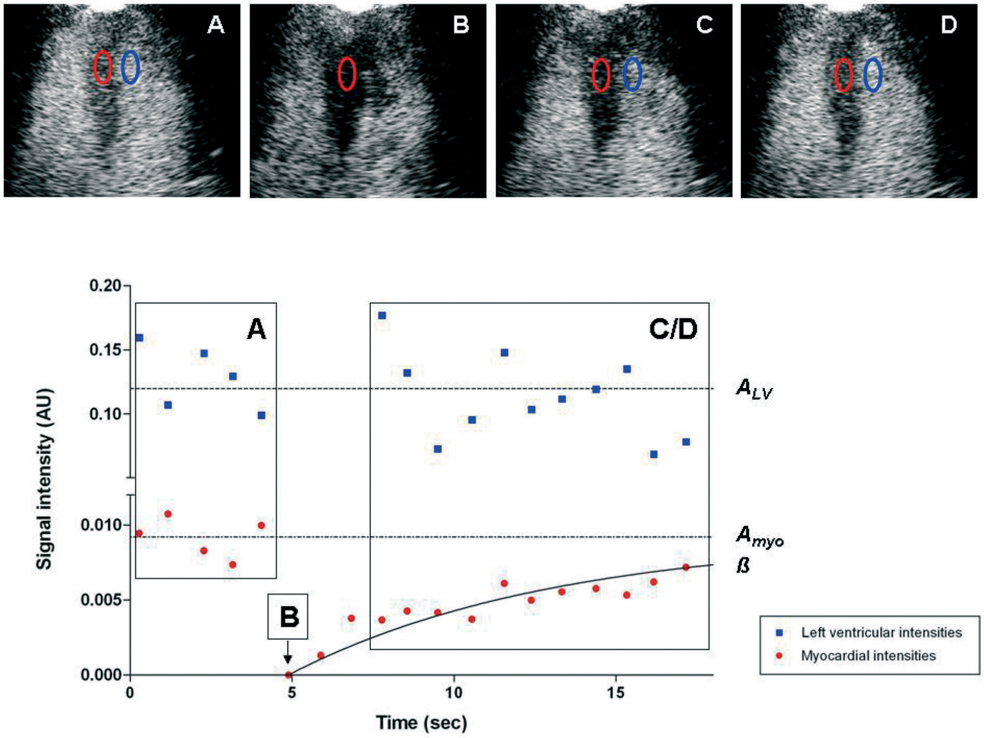

Figure 1. Example of a destruction-replenishment sequence analysis obtained with real-time myocardial contrast echocardiography (apical 4-chamber view, zoomed in on left venticle). Signal intensities are determined by myocardial (red) and ventricular (blue) regions of interest. A: steady state concentration of microbubbles during low mechanical index (MI) impulse; B: complete myocardial contrast destruction directly after high MI impulse; C+D: replenishment of myocardial contrast during low MI imaging. A_{LV}: average left ventricular intensity; A_{myo}: average myocardial steady state intensity; β: rate constant. For further details, see Methods.

Calculated variables

Absolute MBF in ml min^{-1} g^{-1} was calculated using the quantification algorithm of Vogel *et al.*[14]:

$$MBF = rBV \cdot \frac{\beta}{\rho T} = \frac{A_{myo}}{A_{LV}} \cdot \frac{\beta}{\rho T}$$

(tissue density ρ_T was set to 1.05 g ml^{-1}). Increases in MBF in response to adenosine and the CPT were expressed as percentage from MBF at rest (100%). Another calculated variable was the rate-pressure product (RPP), which is an estimate of myocardial oxygen consumption or myocardial work and is calculated by heart rate x systolic blood pressure. An index of coronary vascular resistance (CVR) was derived from the ratio of mean arterial blood pressure to MBF.

Measurement of catecholamines

The systemic response to the cold pressor test at baseline and during the administration of sevoflurane was evaluated by determination of levels of circulating norepinephrine. In venous blood samples taken before the start and two minutes into the CPT, plasma levels of norepinephrine were measured by high-performance liquid chromatography with electrochemical detection.

Statistical analysis

All data are represented as mean values±standard deviation (SD) unless indicated otherwise. In healthy subjects, MBF increases 200 to 300% in response to adenosine and about 30 to 40% in response to sympathetic stimulation by the CPT.[20] Considering a 25% change in myocardial perfusion as relevant, power analysis revealed that thirteen patients should be included to detect this difference with a power of 0.9. Using SPSS statistical software version 15.0 (SPSS Inc., Chicago, Illinois, USA), an unpaired t-test was used to compare catecholamine levels before and after CPT and percent increase in MBF after adenosine and CPT at baseline versus sevoflurane anesthesia. For each unpaired t-test, a Shapiro-Wilk normality test was applied to residuals and all $P > 0.1042$. As stated previously, hemodynamic and myocardial perfusion parameters (β, rBV, MBF) were repeatedly obtained at baseline and during sevoflurane anesthesia. Differences were calculated and changes in hemodynamic and myocardial perfusion parameters were analyzed using a Linear Mixed model with an unstructured covariance matrix in Statistical Analysis Software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). This procedure accounts for the repeated measurements of MBF and hemodynamic parameters. The main assumption of the Linear Mixed model was checked by generating residual plots to see if these were normally distributed. A *P*-value of <0.05 was considered to be statistically significant.

RESULTS

In all thirteen patients MBF measurements were completed successfully on both occasions except for one baseline CPT, which was ceased due to patient discomfort during immersion of the hand. Table 1 shows the baseline characteristics of the study population.

Table 1. Baseline characteristics of study population (n=13)

Variable	
Age, y [a]	43 (28 – 61)
Female/male, n	6/7
Weight, kg	78 ± 16
BMI, kg/m^2	25.5 ± 4.4
SBP, mmHg	120 ± 16
DBP, mmHg	73 ± 6
Fasting glucose, mmol/l	5.0 ± 0.6
Cholesterol, mmol/l	4.6 ± 0.8
HDL, mmol/l	1.4 ± 0.5
LDL, mmol/l	2.6 ± 0.7
Triglycerides, mmol/l	1.1 ± 0.5
Hemoglobin, mmol/l [a]	8.5 (6.7 – 9.7)
Type of surgery	
Ear, nose and throat	5
Urology	2
Gynaecology	2
General (cholecystectomy, ganglion)	4

BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure. [a] Age and hemoglobin are given as mean (range)

Baseline measurements

At baseline, resting MBF was 1.05±0.32 ml min^{-1} g^{-1}, which increased to 3.53±0.75 ml min^{-1} g^{-1} during adenosine-induced hyperemia (P<0.0001; 95% confidence interval (CI) 2.03 to 2.93; Table 2 and Figure 2). In response to adenosine, both rBV (0.099±0.021 ml ml^{-1} to 0.143±0.025 ml ml^{-1}; P=0.0001; 95% CI 0.03 to 0.06) and β (11.1±2.5 min^{-1} to 25.8±5.8 min^{-1}; P<0.0001; 95% CI 11.74 to 17.69) increased compared to rest. Heart rate and RPP increased with infusion of adenosine while blood pressure remained similar (Table 2). During sympathetic stimulation by the CPT, myocardial blood flow increased to 1.53±0.5 ml min^{-1} g^{-1} (P=0.0012 compared to rest; 95% CI 0.25 to 0.76). An increase in heart rate and blood pressure, and a decrease in CVR were also observed compared to rest. Circulating norepinephrine levels did not increase during baseline CPT (Table 3).

Sevoflurane measurements

During sevoflurane anesthesia, resting MBF was similar compared with baseline (1.05±0.28 vs 1.05±0.32 ml min^{-1} g^{-1}; P=0.98; 95% CI -0.18 to 0.18). However, the rBV was lower during anesthesia (0.076±0.015 ml ml^{-1} versus 0.099±0.021 ml ml^{-1} at baseline; P=0.0044; 95% CI 0.01 to 0.04). MBF was preserved because of an increased β (14.6±3.9 min^{-1} versus 11.1±2.5 min^{-1} at baseline; P=0.0005; 95% CI -5.18 to -1.89). Resting blood pressure decreased and heart rate increased compared with baseline values. CVR was statistically similar for both conditions (P=0.06; 95% CI -1.1 to 40.6).

Table 2. Hemodynamic and echocardiographic data at baseline and during sevoflurane anesthesia

Measurement	Rest		Adenosine		CPT	
Baseline						
Heart rate, min^{-1}	64	(58-69)	91	(83-99)‡	69	(64-74)†
SBP, mmHg	116	(108-124)	122	(113-130)	132	(119-144)†
MAP, mmHg	87	(83-91)	91	(87-94)	96	(89-104)*
DBP, mmHg	72	(68-77)	75	(71-79)	79	(73-84)*
RPP, min^{-1} mmHg	7382	(6096-8669)	11098	(9741-12455)‡	9061	(7951-10170)
CVR, mmHg ml^{-1} min^{-1} g^{-1}	92	(72-112)	27	(23-30)‡	65	(50-80)†
Beta, min^{-1}	11.1	(9.6-12.6)	25.8	(22.3-29.3)‡	14.6	(12.2-16.9)*
rBV, ml ml^{-1}	0.099	(0.086-0.112)	0.143	(0.128-0.158)†	0.102	(0.083-0.121)
MBF, ml min^{-1} g^{-1}	1.05	(0.85-1.24)	3.53	(3.08-3.98)‡	1.53	(1.19-1.86)†
Sevoflurane						
Heart rate, min^{-1}	72	(65-80)‖	84	(76-93)†	73	(63-84)
SBP, mmHg	100	(92-109)§	81	(76-86)†#	86	(81-91)†§
MAP, mmHg	71	(65-78)§	57	(53-62)†#	59	(54-64)†§
DBP, mmHg	57	(51-63)§	46	(42-50)†#	46	(39-52)†#
RPP, min^{-1} mmHg	7262	(6294-8231)	6869	(5943-7796)#	6307	(5231-7382)§
CVR, mmHg ml^{-1} min^{-1} g^{-1}	72	(59-85)	26	(23-30)‡	42	(34-50)†‖
Beta, min^{-1}	14.6	(12.3-17.0)§	30.6	(26.2-35.1)‡‖	23.5	(18.3-28.7)†§
rBV, ml ml^{-1}	0.076	(0.067-0.085)§	0.088	(0.073-0.102)§	0.075	(0.061-0.089)‖
MBF, ml min^{-1} g^{-1}	1.05	(0.88-1.22)	2.25	(1.93-2.58)‡§	1.55	(1.24-1.86)†

CPT: cold pressor test; CVR: coronary vascular resistance; DBP: diastolic blood pressure; MAP: mean arterial pressure; MBF: myocardial blood flow; rBV: relative blood volume; RPP: rate-pressure product; SBP: systolic blood pressure. Values are presented as mean (95% confidence interval). The MIXED procedure was used for statistical analysis. * $P<0.05$ versus corresponding value at rest; † $P<0.01$ versus corresponding value at rest; ‡ $P<0.0001$ versus corresponding value at rest; ‖ $P<0.05$ versus corresponding baseline value; § $P<0.01$ versus corresponding baseline value; # $P<0.0001$ versus corresponding baseline value.

Table 3. Levels of circulating catecholamines at rest and during the cold pressor test

	Rest	Cold Pressor Test
Norepinephrine (nmol/L)		
Baseline	2.7 ± 1.1	3.1 ± 1.2
Sevoflurane	1.4 ± 0.3	1.5 ± 0.4

An unpaired t-test was used for statistical analysis.

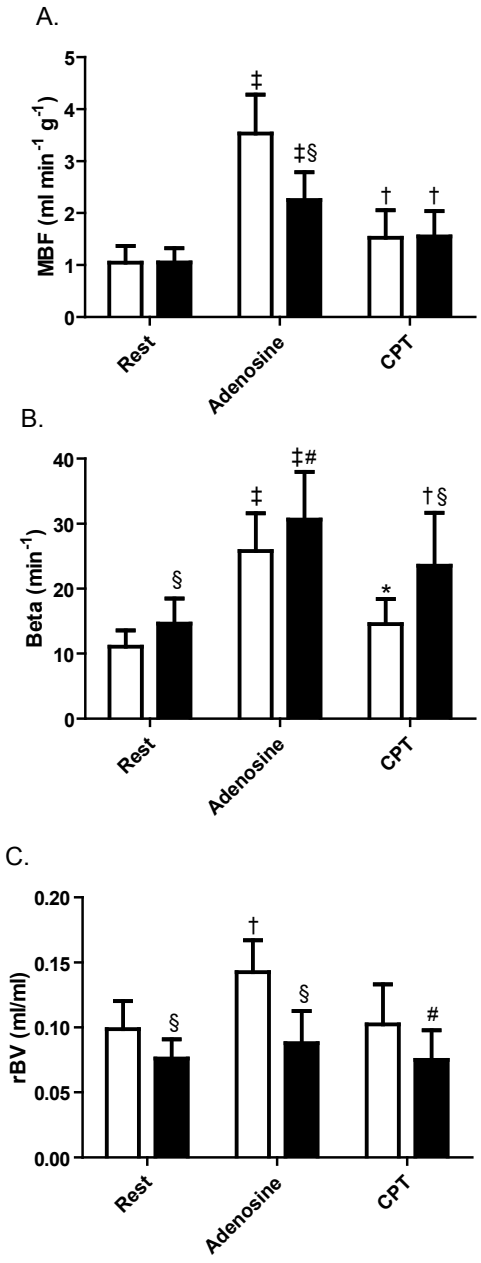

Figure 2. Myocardial perfusion parameters at rest, during adenosine-induced hyperemia and after the cold pressor test (CPT); A: myocardial blood flow (MBF); B: capillary exchange rate (β); C: relative blood volume (rBV). Graphs represent mean±SD. The MIXED procedure was used for statistical analysis. * $P<0.05$ versus corresponding value at rest; † $P<0.01$ versus corresponding value at rest; ‡ $P<0.0001$ versus corresponding value at rest; # $P<0.05$ versus corresponding baseline value; § $P<0.01$ versus corresponding baseline value.

Adenosine infusion during anesthesia increased MBF to 2.25±0.53 ml min^{-1} g^{-1}, which was significantly lower than at baseline (*P*=0.0003; 95% CI 0.72 to 1.84). Consequently, a lower percent increase was observed compared with baseline (228% vs 375%; *P*=0.0087; 95% CI 40.8 to 253.5; Figure 3). In contrast with baseline results, blood pressure and RPP decreased during hyperemia. CVR decreased to a similar level as baseline.

The CPT during sevoflurane anesthesia increased MBF and the magnitude of flow increase was similar compared to baseline (153% versus 152%; *P*=0.96; 95% CI -44.2 to 42.2; see Figure 3). Also during CPT the rBV was lower when compared with baseline (*P*=0.03; 95% CI 0.01 to 0.05). However, MBF was maintained by an increased β. Interestingly, the hemodynamic response to the CPT was different from baseline. A decrease in blood pressure and in RPP was observed and the CVR was reduced compared with baseline. Also, circulating norepinephrine levels did not increase during sevoflurane anesthesia.

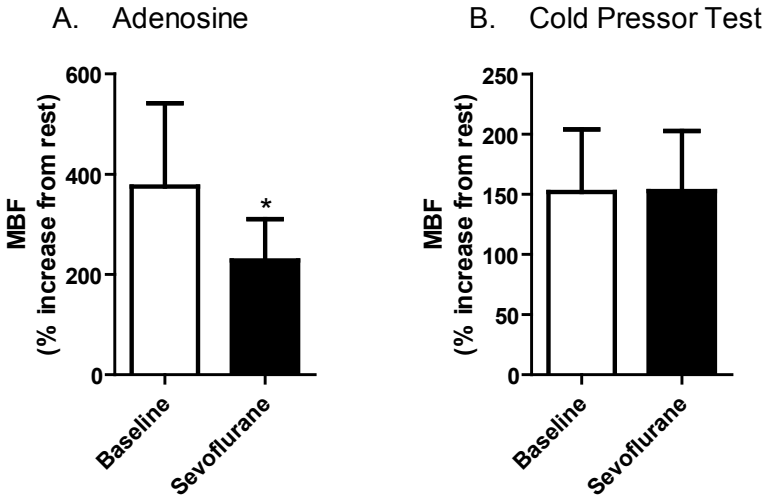

Figure 3. Percent increases in myocardial blood flow (MBF) in response to adenosine-induced hyperemia (A) and the cold pressor test (B) at baseline and during sevoflurane anesthesia. Graphs represent mean±SD. An unpaired t-test was used for statistical analysis. * *P* = 0.0087 versus baseline.

DISCUSSION

Sevoflurane anesthesia preserves myocardial blood flow at rest and during sympathetic stimulation. However, hyperemic myocardial blood flow during 1.0 MAC sevoflurane was lower compared with baseline values without sevoflurane.

Resting myocardial perfusion during sevoflurane anesthesia

The effects of volatile anesthetics on myocardial perfusion in humans have not been well described. One clinical study showed a decrease in myocardial blood flow and oxygen consumption during halothane anesthesia in only 7 healthy patients.[21] A more recent study reported no difference in resting MBF during xenon anesthesia in 6 healthy subjects.[22] Available data on actions of sevoflurane are based on animal studies. Several investigators have reported coronary vasodilation with sevoflurane both in vitro and in vivo.[4,23,24] Furthermore, several studies showed a reduced coronary blood flow during sevoflurane anesthesia, attributed to a decrease in myocardial oxygen consumption and perfusion pressure.[25-27] Instrumented rats demonstrated no alterations in hemodynamics and coronary blood flow in response to sevoflurane administration.[28,29] In contrast, increases in coronary blood flow were reported in dogs when perfusion pressure was kept constant during measurements.[24] In our population, sevoflurane administration resulted in arteriolar vasodilation reflected by an increase in the exchange frequency (β).[30] The lower myocardial blood volume during sevoflurane anesthesia compared to baseline is an interesting finding. It has been shown that, under physiological circumstances, myocardial blood volume remains stable when arteriolar vasomotion is intact.[31,32] Ninety percent of the myocardial blood volume is located in the capillaries, which have a constant length and cannot dilate or constrict due to a lack of smooth muscle. It follows that the myocardial blood volume can only decrease if capillaries are functionally occluded.[33] Whether sevoflurane alone, or in combination with other perioperative factors causes derecruitment of capillaries remains to be elucidated.

Adenosine-induced hyperemia during sevoflurane anesthesia

During adenosine-induced hyperemia, active vasomotor influences are eliminated and myocardial blood flow is mainly dependent on perfusion pressure.[34] At baseline, perfusion pressure remained unaltered and coronary vasodilation resulted in an average MBF increase of 375%. On average, a three to fivefold increase in myocardial blood flow is observed in healthy humans.[2] A significantly lower perfusion pressure was the result of the joint administration of sevoflurane and adenosine. Interestingly, an average 228% increase in myocardial blood flow during sevoflurane anesthesia was observed, suggesting preservation of a substantial vasodilator capacity. In contrast with our data, Gilbert *et al.* demonstrated that the reactive hyperemic response after brief coronary artery occlusion was unaffected by increasing concentrations of isoflurane up to 1.5 MAC, despite reductions in arterial pressure.[35] In the same study, halothane exhausted the vasodilator capacity expressed as the coronary flow reserve (ratio of $MBF_{hyperemia}/MBF_{rest}$) at concentrations of 1.25 – 1.5 MAC, also after correcting for lower perfusion pressures. The mechanism behind the decrease in coronary flow reserve with halothane in that study is difficult to interpret due to the absence of awake measurements and the lack of separate resting and peak flows. Verrier *et al.* reported a greater

coronary flow reserve in dogs anesthetized with low concentrations of halothane compared with nitrous oxide.[36] The lower flow reserve with nitrous oxide may be the result of the higher heart rate and contractility found in that group, changes that are known to alter coronary flow reserve.[37,38] Furthermore, resting coronary blood flow was significantly lower in the halothane group, which increases the maximal achievable flow reserve. However, the mechanism behind reactive hyperemia is complex as other mediators, beside adenosine, are involved as well.[39]
In our population, the decrease in perfusion pressure is a plausible explanation for the lower hyperemic MBF. This hypothesis is supported by Hickey *et al.*, studying the effect of 1.0 MAC halothane, enflurane and isoflurane on coronary vascular reserve in chronically instrumented dogs.[40] Hyperemia was induced with adenosine and diastolic pressures were kept constant. The investigators showed that coronary vascular reserve was not changed by any of the tested anesthetics. Larach *et al.*, investigating coronary flow reserve during sevoflurane administration in isolated rat hearts, confirmed our finding in part.[4] At a constant perfusion pressure, hyperemic coronary blood flow remained unchanged during different sevoflurane concentrations. Also, a comparable degree of coronary vasodilation, indicated by the CVR, was observed at baseline and during anesthesia in our population. This further supports our hypothesis that the reduction in perfusion pressure and the subsequent decrease in rBV are responsible for the decrease in hyperemic MBF. It remains unclear whether this reduction is purely a consequence of the indirect effects of sevoflurane on hemodynamic parameters or also the result of a direct, blunting effect on the recruitment capacity of the capillary network during hyperemia.

Myocardial perfusion in response to sympathetic stimulation

Sympathetic stimulation by the cold pressor test activates α- and β-adrenergic receptors in the heart.[41] Furthermore, pain sensation will induce an increase in adrenomedullary catecholamine release followed by an increase in heart rate, blood pressure and oxygen demand.[42] The net effect of these alterations is coronary vasodilation and an average increase of 40% in myocardial blood flow in healthy humans.[43,44] Our results indicate that during sevoflurane anesthesia, MBF increases in response to sympathetic stimulation despite a decrease in blood pressure and RPP and similar catecholamine levels. Acceleration of erythrocyte passage (increased β) and reduction of coronary vascular resistance indicates arteriolar vasodilation, probably due to adrenergic stimulation via thermal receptors in the skin. The administration of sevoflurane itself and the subsequent decrease in perfusion pressure may have further contributed to the decrease in CVR. The lack of increase in estimated myocardial work in response to sympathetic stimulation might be explained by the blunting effect of sevoflurane on pain sensation. Moffitt and Sethna showed a decrease in coronary blood flow and oxygen demand after sternotomy.[45] In contrast, Kirno *et al.* reported an increase in great cardiac vein flow and oxygen demand during sternotomy.[46] Also, measurements were performed in patients

with coronary artery disease and during different anesthesia techniques, limiting possible comparison with our results.

Limitations

The following limitations should be taken into account in the interpretation of our results. In this in vivo study, interpretation of the exact mechanism behind changes in myocardial perfusion during general anesthesia is limited by the simultaneous influence of sevoflurane on the myocardial vasculature as well as on left ventricular contractility, systemic vascular resistance and sympathetic nerve activity.[3] In this study, we did not control hemodynamic parameters during the measurements. In addition, patients were breathing spontaneously via a laryngeal mask, which may reduce the accuracy of end-tidal CO_2 values because of possible leaks. The reduced sympathetic response of laryngeal mask insertion compared to endotracheal intubation may limit generalized translation of our results. Also, it would have been preferable to measure myocardial oxygen consumption directly from the coronary sinus. The noninvasive rate-pressure product used in this study is a simplified index of myocardial metabolism with limited reliability. It remains, however, widely used in clinical studies with a noninvasive character.

Myocardial perfusion is a dynamic process that is dependent on many physiologic and psychological factors.[1] Therefore, correct timing of experiments is crucial. Unfortunately, due to logistical reasons it was not always possible to perform baseline measurements at the same day prior to surgery. The variation of several days between patients may have influenced our results. However, possible bias was minimized by performing all experiments early in the morning after overnight fasting and in the same order (autonomic function tests, ECG, TTE, perfusion measurements). Also, experiments during sevoflurane anesthesia were always performed at 8 AM in the morning since these patients were scheduled as first on the surgery programme of that day. For logistical reasons, we did not repeat resting MCE after adenosine-induced hyperemia and before CPT-induced sympathetic stimulation.

The cold pressor test is a widely used method for evoking sympathetic stimulation in awake patients but its effects under anesthesia are less well defined. Our results indicate that changes occur on a microvascular level compared to the resting situation, which led to an increase in MBF. Changes in hemodynamic parameters are however different from what would be expected and cannot be explained in the current study design.

Finally, the cardiovascular status of the study population was confirmed by physical examination, laboratory investigation, ECG and routine TTE. Due to the invasive nature, coronary angiography was not performed and therefore we cannot exclude the presence of mild atherosclerosis. However, it is unlikely that unknown atherosclerosis affected our results because of the absence of cardiovascular risk factors and the normal baseline myocardial flow reserves.

CONCLUSION

Our data show that myocardial perfusion at rest is unaffected by sevoflurane anesthesia, despite an apparent decrease in myocardial blood volume. Furthermore, hyperemic MBF (representing myocardial flow reserve), is reduced during anesthesia, most likely caused by a decrease in perfusion pressure. Finally, sympathetic stimulation during sevoflurane resulted in a similar increase in myocardial blood flow compared to baseline. Whether the observed changes are the result of a direct effect of sevoflurane on the myocardial vasculature, or purely a consequence of indirect hemodynamic alterations remains to be elucidated in future studies.

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TO THE EDITOR: THE EFFECT OF SEVOFLURANE ON CORONARY FLOW RESERVE

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In a recent paper, Bulte *et al.*[1] described studies in healthy humans to determine the effect of general anesthesia with sevoflurane on the myocardial hyperemia (an index of coronary flow reserve (CFR)) induced by an IV infusion of adenosine. The authors reported that sevoflurane anesthesia caused a 36% decrease in the myocardial hyperemia. An analysis of their data indicates that the decrease in the hyperemic response can be entirely explained by a proportional decrease in mean arterial blood pressure, i.e., perfusion pressure, which was caused by adenosine during sevoflurane anesthesia. It is standard to evaluate CFR using an intracoronary infusion of a vasodilating drug such as papaverine or the reactive hyperemic response (the transient increase in blood flow that follows an interval of arterial occlusion) in order to avoid systemic hemodynamic effects.[2,3] If either of these approaches was used by Bulte *et al.*, no change in the hyperemic response would have been evident. Bulte *et al.* also reported that sevoflurane was a coronary vasodilator in the human subjects of their study which confirmed previous findings in canine models.[4,5]

The physiological significance of a reduced CFR was not addressed by Bulte *et al.* and requires comment. Myocardial oxygen uptake is determined by coronary blood flow and myocardial oxygen extraction. Since oxygen extraction is nearly maximum at rest, increases in myocardial oxygen uptake are dependent on essentially proportional increases in coronary blood flow.[6] Thus, one might conclude that a reduced CFR would necessarily render the myocardium more vulnerable to ischemia when faced with an augmented cardiac workload or a decrease in arterial pressure. This is the case when the reduced CFR is due to the metabolic vasodilation that accompanies a coronary stenosis or a reduced arterial oxygen (O2) content, e.g., hypoxemia or hemodilution.[2,3] However, it would not be case when the reduced CFR is the result of pharmacological vasodilation. This situation is characterized by "luxuriant perfusion" leading to a concomitant reduction in O2 extraction.[7] A consequence is the establishment of an O2 extraction reserve which can offset a blunted blood flow response during an increased myocardial O2 demand.

Studies in animal models have demonstrated that a decreased CFR can have important adverse effects on the regional distribution of myocardial blood flow.[8] For example, when the CFR is normal, severe tachycardia is accompanied by a transmurally uniform increase in myocardial blood flow, but when CFR is limited, only mild tachycardia may produce subendocardial ischemia. This effect would be relevant regardless of the etiology of the decreased CFR.

Bulte *et al.* obtained measurements of myocardial blood flow using myocardial contrast echocardiography. They validated this technique in a previous study by demonstrating a good correlation to results obtained with positron emission tomography.[9]

Although the myocardial contrast echocardiography technique would appear to have clinical value in the diagnosis and management of coronary artery disease, its investigatory potential will be realized only if it is applied to thoughtfully conceived and well-designed studies of coronary physiology, pathophysiology, and pharmacology.

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IN RESPONSE

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We determined flow reserve in otherwise healthy patients as a measure of myocardial microvascular responsiveness.[1] The vasodilator response of the myocardium to infusion of adenosine is largely mediated by vascular smooth muscle relaxation and partly by endothelial release of nitric oxide.[2,3] As Crystal[4] points out, a decreased flow reserve may become clinically relevant for our population in situations where hypoxemia and tachycardia are combined with low perfusion pressures, and he suggests that a reduced mean arterial blood pressure is a likely explanation for a lower flow reserve during sevoflurane anesthesia. Also, he expects that an intracoronary infusion of a vasodilatory drug, such as papaverine, or a reactive hyperemic response could disentangle the interaction between system hemodynamics and myocardial microvascular perfusion. Although both interventions are indeed interesting suggestions, our specific goal for the current study was to gain insight into myocardial microcirculatory changes during general anesthesia in a clinically relevant scenario in which hemodynamic variables were not controlled for.

Two important features of myocardial contrast echocardiography used in this study make it a suitable imaging modality. First, the noninvasive and bedside character allows measurements in cardiovascularly healthy patients, both with and without anesthesia. Second, and perhaps most importantly, contrast echocardiography allows a unique glance into the behavior of the myocardial microvasculature in the perioperative setting, which is not feasible with other imaging techniques like positron-emission tomography.[5] During continuous infusion of an ultrasound contrast agent consisting of microbubbles, a steady-state concentration is reached after a few minutes. At that moment, tissue signal intensity reflects myocardial blood volume.[6] Subsequently, measuring the rate at which microbubbles replenish myocardial tissue after their destruction provides an estimate of the exchange rate. The product of myocardial blood volume and exchange rate reflects myocardial blood flow.

To evaluate the potential value of myocardial contrast echocardiography for clinical and research purposes, we first investigated the myocardial microvascular behavior in cardiovascularly healthy patients with and without anesthesia. After this necessary first step, we are currently focusing on patients with preexisting reduced myocardial flow reserves using the same technique. As such, we hope to gain more insight into the complex interaction of general anesthesia, perioperative hemodynamics, and preexisting myocardial perfusion abnormalities.

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